PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 001107.00350	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US03/17262	International filing date *(day/month/year)* 04 June 2003 (04.06.2003)	Priority date *(day/month/year)* 06 June 2002 (06.06.2002)
International Patent Classification (IPC) or national classification and IPC IPC(7): C12Q 1/68; C12P 19/34; C07H 21/04 and US Cl.: 435/6, 91.1, 91.21; 536/24.33		
Applicant JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 December 2003 (31.12.2003)	18 February 2005 (18.02.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Suryaprabha Chunduru Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/17262

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-12 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 13-16 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages 1-4 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages NONE

☐ the claims, Nos. NONE

☐ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US03/17262

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	4, 10, 14, 23-25, 30, 35	YES
	Claims	1-3,5-9,12,13,15,16,19-22,26-29 and 31-34	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	4, 10, 14, 17-18, 23-25, 30, 35	NO
Industrial Applicability (IA)	Claims	1-35	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS
Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-3, 5-9, 12-13, 15-16, 34 lack novelty under PCT Article 33(2) as being anticipated by Lapidus et al. (USPN. 5,928,870).

Lapidus et al. teach a method of associating genotype with a phenotype (genomic instability) comprising (i) determining levels of expression of alleles (enumerate amount of gene or genes of a genetic region) in a first population (sample) (see col. 2, line 58-60, col. 3, line 11-15); (ii) comparing the levels of expression of alleles with a second population (known control sample); identifying the levels of expression of alleles whose expression differs statistically significant manner between the first and second population as having an association with the phenotype (see col. 2, line 60-67, col. 3, line 15-27); Lapidus et al. also teach (a) that the phenotype comprises, disease susceptibility or a disease (cancer or precancer), (genetic abnormality), status of heterozygosity of the genes of interest based on sequence variation including insertion, deletion, SNP (see col. 2, line 39-57); (b) determination of level of expression using dye terminators (see col. 3, line 42-54). Thus the disclosure of Lapidus et al. meets the limitations in the instant claims and therefore the instant claims lack novelty under PCT Article 33(2).

Claims 19-22, 26-29, 31-33 lack novelty under PCT Article 33(2) as being anticipated by Lapidus et al. (USPN. 6,146,828).

Lapidus et al. teach a method for measuring allelic expression variation in a non-imprinted individual, comprising (i) reverse transcribing and amplifying mRNA from an individual to form a first cDNA and a second cDNA (see col. 4, line 28-51, col. 6, line 15-45, col. 7, line 1-38); (ii) hybridizing primers to cDNA and labeling the primers using single base extension (see col. 7, line 7-67); (iii) comparing the amounts of differentially labeled primers, wherein the statistically significant difference between the first and second primers are indicative of first and second allele (see col. 4, line 20-67, col. 6, line 64-67, see col. 12, line 15-60); Lapidus et al. also teach fluorescent dye terminators (see col. 10, line 22-38); single base extension (see col. 7, line 7-21); detecting alteration in expression variation (see col. 6, line 16-32). Thus the disclosure of Lapidus et al. meets the limitations in the instant claims and therefore the instant claims lack novelty under PCT Article 33(2).

Claims 4, 10, 14, 17-18, 23-25, 30-35, lack an inventive step under PCT Article 33(3) as being obvious over Lapidus et al. (USPN. Lapidus et al. (USPN. 5,928,870) ('870) in view of Lapidus et al. (USPN. 6,146,828) ('828).

Lapidus et al. ('870) teach a method of associating genotype with a phenotype (genomic instability) comprising (i) determining levels of expression of alleles (enumerate amount of gene or genes of a genetic region) in a first population (sample) (see col. 2, line 58-60, col. 3, line 11-15); (ii) comparing the levels of expression of alleles with a second population (known control sample); identifying the levels of expression of alleles whose expression differs statistically significant manner between the first and second population as having an association with the phenotype (see col. 2, line 60-67, col. 3, line 15-27); Lapidus et al. ('870) also teach (a) that the

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

phenotype comprises, disease susceptibility or a disease (cancer or precancer), genetic abnormality, status of heterozygosity of the genes of interest based on sequence variation including insertion, deletion, (see col. 2, line 39-57); (b) determination of level of expression using dye terminators (see col. 3, line 42-54). However, Lapidus et al. ('870) did not teach phenotype as birth defect, determining haplotype or SNP, fluorescent dye terminators.

Lapidus et al. ('828) teach a method for measuring allelic expression variation in a non-imprinted individual, comprising (i) reverse transcribing and amplifying mRNA from an individual to form a first cDNA and a second cDNA (see col. 4, line 28-51, col. 6, line 15-45, col. 7, line 1-38); (ii) hybridizing primers to cDNA and labeling the primers using single base extension (see col. 7, line 7-67); (iii) comparing the amounts of differentially labeled primers, wherein the statistically significant difference between the first and second primers are indicative of first and second allele (see col. 4, line 20-67, col. 6, line 64-67, see col. 12, line 15-60); Lapidus et al. ('828) also teach fluorescent dye terminators (see col. 10, line 22-38); single base extension (see col. 7, line 7-21); detecting alteration in expression variation (see col. 6, line 16-32).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to modify a method associating a genotype with a phenotype as taught by Lapidus et al. ('870) with incorporation of fluorescent dye terminators as taught by Lapidus et al. ('828) to achieve expected advantage of developing a an improved and sensitive molecular diagnostic method for identifying genetic variation. An ordinary practitioner would have been motivated to modify the method as taught by ('870) with the incorporation of a step of identifying birth defects, haplotype and use of fluorescent dye terminators as taught by ('828) for the purpose of determining a genetic variation with enhanced sensitivity and specificity. Therefore the instant claims lack inventive step under PCT Article 33(3).

---------- NEW CITATIONS ----------

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NOTE OF INFORMAL COMMUNICATION WITH THE APPLICANT

(PCT Rule 66.6)

International application No.	Applicant's or agent's file reference	Date of informal communication *(day/month/year)*
PCT/US03/17262	001107.00350	
Applicant JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE		

Communication

☒ by telephone

☐ personal

Participants

☐ Identity checked ☒ authorization checked ☐ personally known

☐ Applicant: JO/HNS, HOPKINS UNIVERSITY SCHOOL OF MEDICINE

☒ Agent: Sarah Kagan

☐ Examiner(s): Suryaprabha Chunduru

Summary of communication:

Examiner telephoned to Sarah Kagan, Applicant's Attorney, on February 18, 2005. Applicants' Attorney agreeded and has given authorization to do PCT-409 instead of 408, to expedite the process.

☐ ~~An extension of time limit is granted (Form PCT/IPEA/427.~~

☒ A copy of this note is being sent to the applicant with Form ~~PCT/IPEA/429.~~ PCT/IPEA/424.

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Authorized officer

Suryaprabha Chunduru

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Form PCT/IPEA/428 (July 1992)